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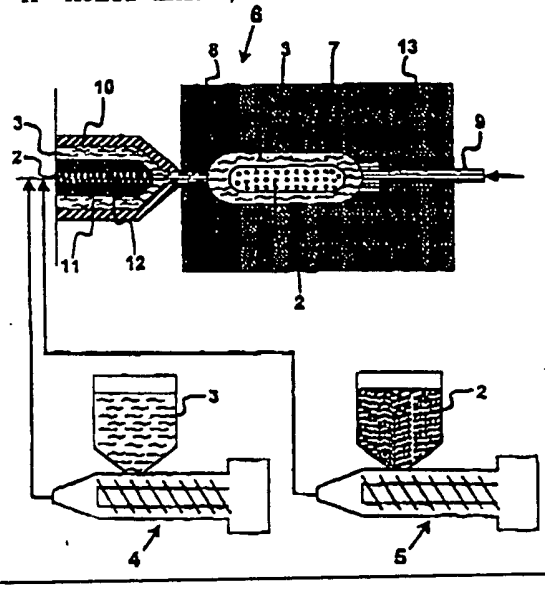
(54) Title: METHOD AND DEVICE FOR PRODUCING A MULTI-LAYER, PHYSIOLOGICALLY TOLERATED PRESENTATION FORM

(57) Abstract

The invention relates to a multi-layer, physiologically tolerated presentation form for medicines, etc., which is produced using a method according to which a core component (2) and a coating component(3) are injected into a shared tool cavity (7) in such a way that the core component is fully coated by the coating component. At least the coating component made of a polymeric, preferably biopolymeric, material is processed thermoplastically. This method allows for the simultaneous production and filling of a presentation form with considerably simpler means and using a broader ranger of materials. More particularly, even coatings made of hard material can be produced and filled seamlessly.



Method and device for producing a multi-layer, physiologically tolerated presentation form

The invention relates to a process for the production of a multi-layer, physiologically tolerated presentation form in accordance with the main concept of Claim 1. This type of presentation form is used above all for the administration of medications. It can however also be used to contain dietetic foods or even only pure luxury items. The active component is as a rule contained in the core component, with the coating component primarily displaying a protective function. For medications, the coating component is also used to achieve a delayed action.

Presentation forms of the type referred to appear above all as capsules made of starch, gelatin or the like. Numerous methods for the production of capsules are already known, such as for example the rotary die method for soft gelatin capsules or the dipping method for hard gelatin capsules. For hard gelatin capsules, the production of the hard outer shell of the capsule in an injection molding method (EP-A-118 240) is also known. All the methods known up to now however have the disadvantage that processes are involved that only lead to the final presentation form in several, sometimes costly steps. Sometimes considerable waste of material results, such as for example in the rotary die method and in the rest the utilization of substances used, depending on the method used at the time, is greatly limited.

GB-A-2 207 335 describes the production of an annular presentation form for the controlled release of a therapeutically active substance in the human or animal body. The ring is formed from a coextruded filament of material consisting of a core material and a coating material, with the two ends of the filament of material being bonded together. Clearly, several operating steps are necessary for this, namely coextrusion of a continuous filament of material, cutting to length of a part-filament, and putting together the part filament.

WO 89/12 442 relates to a presentation form for the treatment of fish. It consists of a coextruded hollow object made of an animal or plant material and an active substance completely enclosed therein. However, the hollow object also contains an air inclusion, so that the structure floats on the surface of the water and is accepted better by the fish. In order to achieve the desired water-tightness, the coextruded filament of material must be formed into closed chambers in another process.

WO 97/15 293 discloses a method for the production of multi-layer, solid forms of medication for oral or rectal administration. The product is first extruded in two layers from a common coextrusion tool and then by means of press bars or press rollers squeezed off to capsule-like structures. Clearly, press seams similar to those in the rotary die method result from this.

US-A-4,352,823 concerns a coextruded chewing gum consisting of a relatively soft core mass and a dry outer coating of harder material. Apart from the fact that the coextrudate subsequently has to be molded into packageable objects this technical system cannot be transferred to the production of a physiologically tolerated presentation form.

Finally, through US-A-5,650,232 a method for the production of seamless, two-phase capsules was made known. In this, two filaments of material are likewise coextruded in a common nozzle. The extrudate falls by gravity from the extrusion nozzle, whereby because of the interfacial surface tension objects are formed in which the outer coating completely surrounds the core material. Very narrow limits are set in this method with respect to the material properties to be taken into consideration. Besides, there is no control over the final outer contour of the capsules.

It is therefore an objective of the invention to provide a method of the type referred to at the beginning that considerably simplifies the operating process and by means of which a wider spectrum of substances can be processed. In addition, seamless objects with phases that are as homogeneous as possible should be produced. This objective is solved with a method that displays the characteristics in Claim 1.

The injection of the core component and the coating component into a common mold cavity has the advantage that it involves an operating process that in contrast to the coextrusion methods cited leads directly to the finished product. The thermoplastic processing of at least the coating component can be effectuated by relatively simple means. With the method presented here, capsules can in practice be produced and filled in a single operation, with the hard outer coating displaying no seam like that in the known two-piece capsules. The outer shape of the capsule can be chosen as desired within a wide bandwidth with respect to diameter and length and materials can also be injected that cannot for example be processed in the rotary die method. In this way, the still widely used gelatin can be replaced by a lower-priced and more easily produced biopolymer.

The preparation and processing of biopolymers for their conversion to an injectable state are described in EP-A-118 240 and WO 90/14938 in the example of starches. In this regard, and especially for the definitions of the expressions "melt streams" and "plastic" or "thermoplastic," these two documents should be expressly referred to.

Preferably, the core component is prepared in a first feeding device and the coating component in the thermoplastic state in a second feeding device. Then the two components are injected simultaneously or sequentially into the mold cavity in such a way that there, at the latest the core component is completely surrounded by the coating component. Finally, the injected molded object is cooled down and ejected after the mold cavity is opened. Obviously, the core

component can be surrounded by several coating components. Also, the core component itself could be split up into several phases.

The core component and the coating component can thereby be injected into the mold cavity as separate melt streams by way of a common injection head. The complete covering of the core component then takes place in the mold cavity. It is however also conceivable that the two components are injected into the mold cavity as a common melt stream by way of a common injection head. For this purpose, the melt stream of the coating component must be injected at the common injection head at regular intervals with material of the core component.

The core component in the injection head is thus already surrounded by the coating component, with the common melt stream being injected into the opened mold cavity and the external shape being achieved by closing the slide plate.

Alternatively, however, the mold cavity can also be first completely filled with the coating component by way of an injection aperture. Then the core component is injected by way of an injection needle into the coating component or into the mold cavity, with the coating component thus displaced flowing out of the mold cavity by way of the injection aperture. It would also be conceivable to encapsulate very low viscosity substances that cannot be processed thermoplastically.

Preferably, at least the coating component is prepared thermoplastically in an extruder, with the injection pressure being created at the extruder. These kinds of extruders with screw plungers are already known for example from the injection molding technology for plastic materials. On the other hand, low-viscosity core components are advantageously metered in by means of a metering reciprocating pump. The amounts to be injected can thereby be very precisely determined.

The invention also relates to a device for the production of a multilayer physiologically tolerated presentation form which is characterized by the features in Claim 9. The molds used in this are outfitted differently depending on the method chosen. A hot channel injection mold can be involved, as is known in similar form for the injection of plastic articles. Particular attention is then to be directed to the discharge device so that the relatively sensitive molded body is not damaged on discharge.

Alternatively, however, the mold can also be provided with special injection heads, slide bars and injection needles.

The presentation form obtained using the method described can be so constituted that it can be assimilated orally, rectally or vaginally by the human or animal body. As in conventional presentation forms, the external appearance, the taste or the surface finish can be

influenced by appropriate adjuvants. The core component and the coating component are preferably completely absorbable in a physiological environment.

The core component can exist in paste or liquid form or as a colloidal system. Possible in particular are dispersions, suspensions, emulsions and solid or liquid foams. Moreover, the core component preferably contains at least one pharmaceutically active substance or another biologically active substance. It is however also conceivable that the coating component likewise has an active substance that if necessary enters into an interaction together with the active substance of the core component.

Other advantages result when the coating component contains a retardant in dissolved form for the delayed release of the active substance in the gastro-intestinal tract. The supplementary coating of the finished capsule, common up to now, is then completely omitted.

The coating component basically consists of physiologically tolerated substances, preferably of a synthetic polymer or biopolymer, in particular

- polysaccharides from among the polyglucosans such as for example crystal starches and natural cellulose; polysaccharides from among the polygalactomannans such as for example natural guar or tara gum, polysaccharides from among the glucomannans, and also polysaccharides such as pectins, algic acid, alginates, chitin, chitosan, and gum arabic;

- oligosaccharides from among the modified polysaccharides already cited, particularly thermally, enzymatically, acid-hydrolytically, oxidatively or mechanically depolymerized starches or cellulose, swell-starches, etc.;

- oligo -and polysaccharide derivatives such as for example esters, ethers and acetates of the substances already named;

- proteins such as albumin, casein, glutin, zeins;

- protein derivatives such as amides, esters and Schiff bases;

- natural esters such as shellac;

- polyesters such as succinic acid, lactic acid, butyric acid, fatty acid esters of alkanols, polylactones [typo in original];

- polyterpenes such as polyisoprenes,

in combination with softeners such as water, alcohol, acids, esters and ethers.

Depending on the purpose of the application, these substances can be relatively easily thermoplastically prepared or processed.

Examples of executions of the invention are shown in the drawing and will be described in more detail below.

Figure 1 shows the diagrammatic representation of an injection mold with two extruders,

Figure 2 shows a cross-section through a typical presentation form,

Figure 3 shows a cross-section through an alternative injection mold in a first operating phase,

Figure 4 shows the injection mold as in Figure 3 in a second operating phase, and

Figure 5 shows another execution example of an injection mold for the separate injection of the core component.

Figure 1 shows, greatly simplified, an injection mold 6 consisting of a mold block 13 and an injection plate 8, which together form the mold cavity 7. Injection plate and mold block can be moved away from each other using means, not shown in detail here, for opening the mold cavity 7. The ejection of the finished molded body results by way of an ejector 9.

Adjacent to the injection plate 8 there is a nozzle head 10, which is provided with an outer injection channel 11 and an inner injection channel 12. The injection channels are respectively connected to a first extruder 4 for the coating component 3 and to a second extruder 5 for the core component 2.

The two components are prepared thermoplastically in the extruders and injected by way of the nozzle head 10 sequentially in separate melt streams into the mold cavity 7. For this, preferably, first a metered amount of the coating component 3 and then a metered amount of core component 2 are injected under a specific injection pressure. The injection head is shown greatly simplified. In reality, the structural components of the head, displaceable relative to each other, have a valve function, with a valve needle also being provided in the center. A multi-channel injection head of this type is for example described in EP-A-647 514. Of course, depending on the construction, several coating components can be injected on top of each other. By the correct selection of the relative viscosity, the temperature, and the rate of flow of the two components, as well as by a very precise determination of the metered volumes, on one hand a complete covering of the core component in the mold cavity is achieved, and on the other the mixing of the two components before hardening is prevented. It has also been shown to be particularly advantageous, after the injection of the core component into the coating component, to again inject a

small amount of coating component, so as to assure a complete covering also in the area of the injection aperture. After the cooling of the molded product, the mold is opened and the capsule 1 shown in Figure 2 is discharged from the mold cavity by means of the ejector 9. Of course, each mold is provided with several cavities and the opening and closing processes take place automatically, so that an economical operation is possible.

The parting plane of the mold is chosen so that the molded product is not taken out on opening, but remains in the mold block 13. Of course, the outer contour is also to be taken into consideration here, with all current capsule shapes, such as oblongs, spheres, ampules or special shapes, being injectable.

In the execution example in accordance with Figures 3 and 4, the two components are injected in a common melt stream into the mold cavity. In place of the usual injection plate, there is a slide plate 14 with at least two sliders 15, 15', that can be displaced in the direction of the arrow a in a slide guide 16. The closed slides likewise form part of the periphery 17 of the mold cavity, as well as a back-flow aperture 23. In the open state, as in Figure 4, the slides 15, 15' form an injection aperture, the cross-section of which approximately corresponds to the largest cross-section of the mold cavity.

Adjacent to the slide plate 14 there is a main injection channel 18, that is connected with an extruder, not shown here, for the coating component 3. On the side, the main injection channel 18 is provided with a side injection channel 19 that is connected to another extruder for the core component 2. The side injection channel is provided with a needle 20, displaceable in the direction of the arrow b, the tip of which can be inserted into the main injection channel 18.

In the operating state in accordance with Figure 3, the slides 15, 15' are closed until the molded product already injected into the cavity has cooled down. At the same time, at the main injection channel 18 with advanced injection needle 20 a specific amount of the core component 2 is already injected into the coating component 3. A bubble 21 is thus formed that is completely surrounded by the coating component.

After the discharge of the finished molded product from the mold cavity, the two slides 15, 15' are opened and the two components are pressed into the mold cavity as a common melt stream. Because of the thus resulting entrance aperture, the common melt stream does not have to pass through narrow places, so that the bubble 21 retains its shape. For the injection of the melt stream, the needle 20 is retracted from the main injection channel 18.

The final form of the capsule is then defined by bringing together the two slides 15, 15', with displaced material of the coating component 3 being able to flow back through the back-flow aperture 23. A very

low viscosity component that cannot be prepared in an extruder could also be injected by way of the side injection channel 19. In this type of case, there is advantageously a metering reciprocating pump instead of the extruder.

In the execution example in accordance with Figure 5, a standard injection plate is provided that is connected to a main injection channel 18. The coating component is injected into the cavity by way of this channel. The injection of the core component occurs at the side with a needle 25 directly into the cavity or into the coating component. For this purpose the needle 25 can also be displaced in the direction of the arrow c. The core component 2 is metered in by means of a metering reciprocating pump 24.

In operation, with a closed mold, the mold cavity 7 is first completely filled with the coating component 3 by way of the main injection channel 18. In a next step, the core component is injected by way of the advanced injection needle 25, with part of the coating component being displaced and flowing back by way of the back-flow aperture 23. For the cooling of the molded body, the needle 25 is retracted. Obviously the injection pressure for the core component 2 must be greater than the pressure on the main channel 18. The invention will be further documented below by means of different examples of executions.

Examples:

Example 1

6.5 kg/hr natural potato starch (st) with a water content of 6% and 3.5 kg/hr 98 to 101% glycerol (gly) (see Deutsches Arzneimittelbuch) are fed into the first of the two extruders of the total unit. The second extruder is charged with 20 kg/hr polyethylene glycol (PEG) 6000 (Macrogol 6000 DAB) UNITED STATES PHARMACOPEIA (USP) with 0.2 kg/hr hydrocortisone acetate (USP). The melt from the first extruder is injected at 150°C and that of the second extruder at 65°C. The injection pressure is 50 bars in both extruders. 3000 presentation forms per hour are obtained with an injection mold containing 16 cavities.

For the performance of in vitro studies, the oval-shaped presentation forms are dissolved in 0.1N hydrochloric acid at 36°C. 90% of the material of the presentation form is dissolved in 30 minutes (solution time).

In the following examples, the above-mentioned contents and parameters are varied:

Examples 2 - 4:

Example	Extruder 1 components T (°C)	Extruder 2 components T (°C)	Solution time for > 90%
2	6 kg st + 3 kg gly 160	18 kg PEG + 0.05 kg of (1) 40	60 min
3	5 kg of (2) + 2 kg of (3) 130	20 kg of (4) + 2 kg of (5) 100	60 min
4	6 kg of (6) + 1 kg gly 180	10 kg of (7) + 3 kg of (8) 100	60 min

(1) Unmicronized Nifedipin (USP); (2) Guar gum; (3) 25 parts by weight of mono-, di-, tri-ethyl esters of citric acid + 1 part by weight peppermint oil + 4 parts by weight peppermint flavor; (4) Acetaminophen (USP); (5) 1 part by weight N-methyl-2-pyrrolidone (Pharmasolve USP) + 1 part by weight Crospovidon (USP); (6) gelatin; (7) silicone oil; (8) nystatin.

Example 5 - 6:

In the following examples, two protective coatings were applied and the active substance was added to the third extruder:

Example	Extruder 1 components T (°C)	Extruder 2 components T (°C)	Extruder 3 components T (°C)
5	6 kg st + 3 kg gly 150	0.5 kg of (3) + 0.5 kg of (4) 60	15 kg of (1) + 10 kg of (2 15
6	5 kg of (5) + 1 kg of (6) 180	3 kg of (4) -10	20 kg of (7) + 5 kg of (8) 15

(1) 1 part by weight Cyclosporin A; (2) 1 part by weight 96% ethanol Ph.Eur. + 1 part by weight propylene glycol (USP) + 10 parts by weight Solutol Ph.Eur.; (3) beeswax; (4) hydrogenated soybean oil; (5) hydroxypropylmethyl cellulose; (6) 5 parts by weight propylene glycol (USP) + 10 parts by weight silicon dioxide (USP) + 2 parts by weight iron oxide NF + 2 parts by weight titanium oxide USP; (7) 30 parts by weight calcium ascorbate + 1.7 parts by weight thiamine hydrochloride + 2 parts by weight riboflavin + 1.7 parts by weight pyridoxine hydrochloride + 15 parts by weight niacin + 8 parts by weight calcium pantothenate + 0.2 parts by weight biotin + 0.4 part by weight folic acid + 15 parts by weight DL-α-tocopherol acetate + 15 parts by weight 30% susp β-carotene + 60 parts by weight magnesium carbonate + 60 parts by weight calcium carbonate + 10 parts by weight iron fumarate; (8) 131 parts by weight soybean oil + 35 parts by weight hydrogenated soybean oil + 7.5 parts by weight soybean lecithin + 7.5 parts by weight beeswax.

In comparison to the direct intake of the active substances (cf. 1 to 8), by means of the presentation form with two coating layers a delayed release and solution of the active substances (delayed action) is achieved.

Patent Claims

1. Process for the production of a multilayer, physiologically tolerated presentation form, in particular a capsule in which at least one core component is completely surrounded by at least one coating component, characterized by the injection of the core component (2) and the coating component (3) into a common mold cavity (7), with at least the coating component being prepared thermoplastically.

2. Process in accordance with claim 1, characterized by the fact that

   - the core component is prepared in a first feeding device (4),

   - the coating component in the thermoplastic state is prepared in a second feeding device (5),

   - the core component and the coating component are injected simultaneously or sequentially into the mold cavity in such a way that there, at the latest the core component is completely surrounded by the coating component,

   - and that the injected molded product (1) is cooled down and, after the opening of the mold cavity (7), discharged.

3. Process in accordance with claim 2, characterized by the fact that the core component and the coating component are injected as separate melt streams into the mold cavity (7) by way of a common injection head (10).

4. Process in accordance with claim 2, characterized by the fact that the core component and the coating component are injected as a common melt stream into the mold cavity by way of a common injection head.

5. Process in accordance with claim 4, characterized by the fact that the core component is already surrounded by the coating component in the injection head, with the common melt stream being injected into the opened mold cavity.

6. Process in accordance with claim 2, characterized by the fact that the mold cavity is first completely filled with the coating component by way of an injection aperture and that then the core component is injected into the coating component by way of an injection needle, with the thus displaced coating component flowing out of the mold cavity by way of the injection aperture.

7. Process in accordance with one of the claims 1 to 6, characterized by the fact that at least the coating component is prepared thermoplastically in an extruder and that the injection pressure is created at the extruder.

8. Process in accordance with one of the claims 1 to 7, characterized by the fact that the core component is metered in by means of a metering reciprocating pump.

9. Device for the production of a multilayer, physiologically tolerated presentation form, in particular a capsule, with at least one core component that is completely covered by at least one coating component, in particular for carrying out the process according to one of the claims 1 to 8, characterized by

- a first feeding device (4) for the coating component,
- a second feeding device for the core component,
- a mold (6) with at least one common mold cavity (7) for accommodation of both components,
- a mold actuation for the opening and closing of the mold, and
- a discharge device (9) for the discharge of the finished molded products from the mold cavity.

10. Device in accordance with claim 9, characterized by the fact that at least the first feeding device is an extruder.

11. Device in accordance with claim 9 or 10, characterized by the fact that the second feeding device is a metering reciprocating pump for the metering in of the core component into the mold cavity or into the feed channel of the first feeding device.

12. Device in accordance with one of the claims 9 to 11, characterized by the fact that the mold has a slide plate with at least two slides (15, 15'), which in the closed state form part of the mold cavity and which in the open state form an injection aperture, the cross-section of which corresponds approximately to the largest cross-section of the mold cavity.

13. Device in accordance with one of the claims 9 to 11, characterized by the fact that the mold has an injection needle (25) that can be inserted into the mold cavity for the injection of the core component.

14. Presentation form consisting of several layers of physiologically tolerated substances, in particular a capsule, in which at least one core component is completely encased by at least one coating component, obtained by means of the process according to one of the claims 1 to 8.

15. Presentation form as in claim 14, characterized by the fact that the core component exists in paste or liquid form or as a colloid system and preferably contains a pharmaceutically active substance.

16. Presentation form in accordance with claim 14 or 15, characterized by the fact that the coating component contains in dissolved form a retarding agent for the delayed release of the active substance in the stomach or intestinal tract.

17. Presentation form in accordance with one of the claims 14 to 16, characterized by the fact that the coating component consists of a thermoplastically produced biopolymer, in particular of oligo- and polysaccharides or their derivatives, proteins or their derivatives, natural esters or polymeric esters, or polyterpenes.

Fig. 1

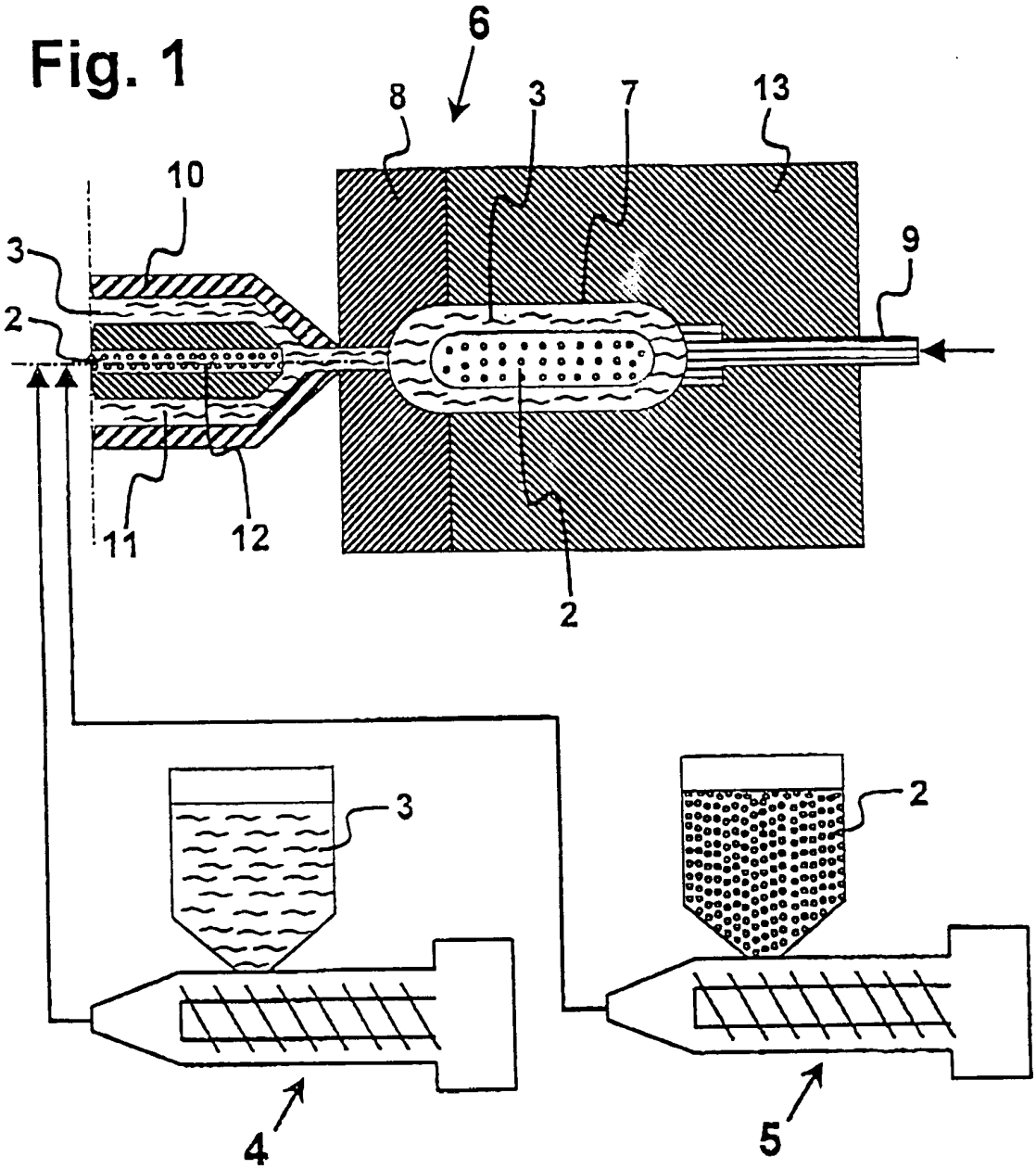


Fig. 2

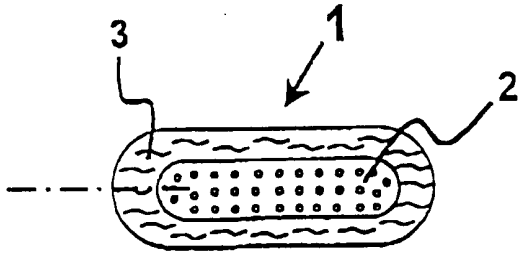


Fig. 3

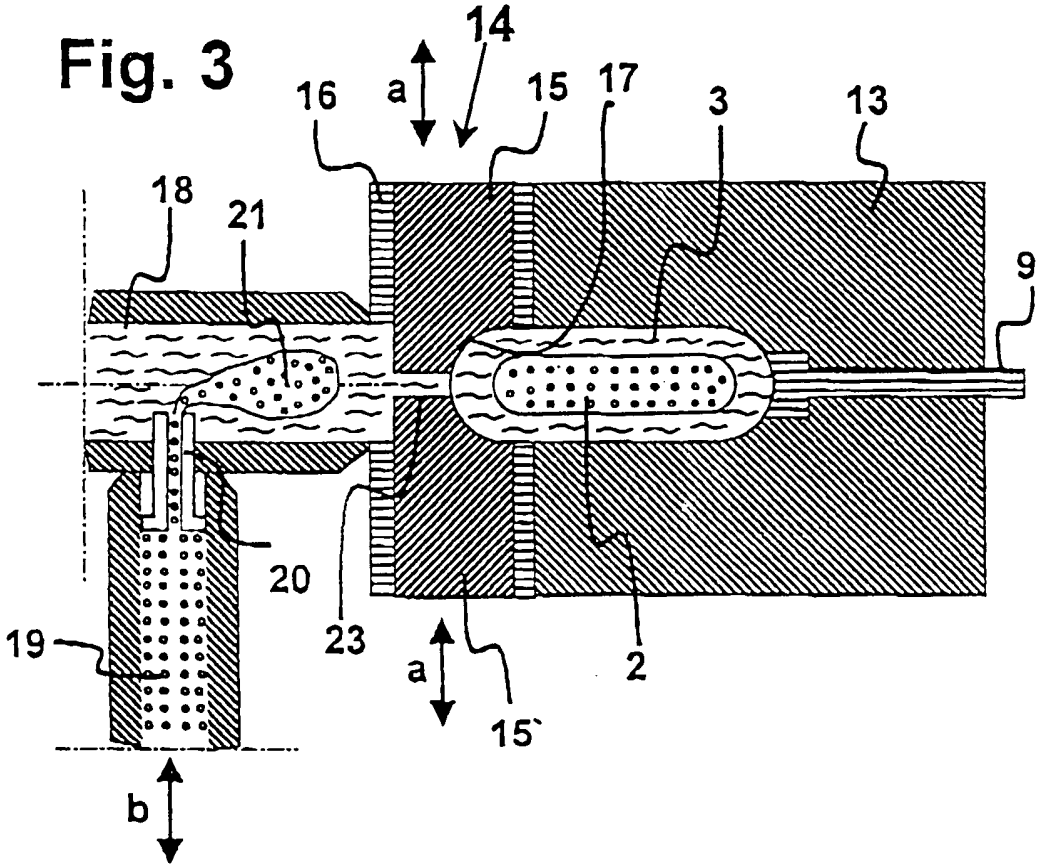


Fig. 4

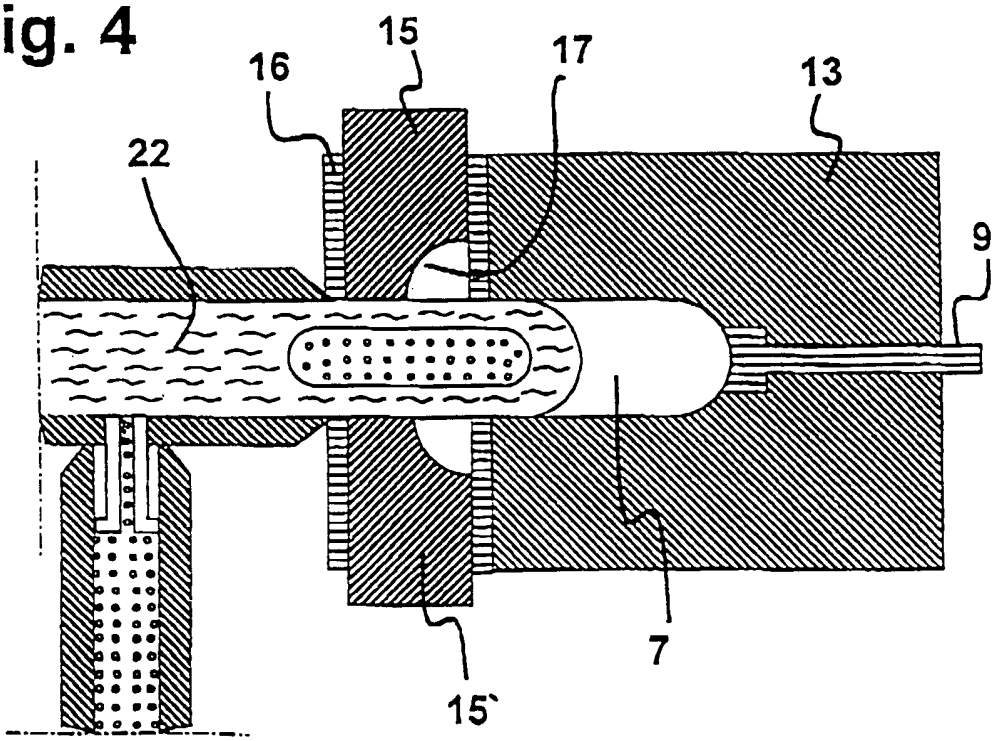


Fig. 5